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Original Article

Formulation and Evaluation of Ocusert Embeded with Ciprofloxacin Loaded Nanoparticles

Faiza Shaikh, Sabiha Khan, Adnan Shaikh, Shruti Shivsharan, Maria Lal, Imran A Sheikh, Mirza Salman Baig*

Anjuman-I-Islam's Kalsekar Technical Campus School of Pharmacy, New Panvel, 410206, Maharashtra, India

**Correspondence E-mail: mirzasalman.pharma@gmail.com*

Abstract

Ophthalmic drug delivery is very challenging. Upon the application of conventional topical ophthalmic formulations, a significant portion of the administered dose goes to waste due to the existence of various ophthalmic barriers. There is a swift elimination of the applied solution from the anterior part of the eyes through the nasolacrimal duct to the nasal cavity. The aim of this study was to develop an ocusert embedded with ciprofloxacin-loaded nanoparticles to increase patient compliance by improving local delivery of the drug. Ciprofloxacin-loaded Eudragit RL PO polymeric nanoparticles were prepared and evaluated for particle properties. These drug-loaded polymeric nanoparticles were embedded in an ocusert made of carboxymethylcellulose. Various properties of ocuserts, like film endurance, surface pH, disintegration time, and sterility, were studied. A drug-loaded nanoparticle-embedded ocusert was found to be a suitable system to improve ophthalmic drug delivery. The nanoparticles' particle size, polydispersity index (PDI), entrapment efficiency, and in vitro drug release were all assessed. The generated ocuserts underwent screening for sterility, drug content, weight variability, folding durability, thickness, surface pH, and disintegration time. In order to gain insight into the process by which drugs release from the formulations, the in vitro drug release from the preparations was examined using a standard Abron Visking semipermeable membrane.

Keywords: *Ciprofloxacin, Carboxymethyl cellulose, CMC, Eudragit Polymeric nanoparticles, Ocular insert, Ocusert*

Introduction

The usual method for treating eye infections is the instillation of aqueous antibiotic solutions (eye drops) directly onto the ocular surface (Watson *et al.*, 2018; Mandal *et al.*, 2022). However, this approach has limitations because the antibiotics don't stay in the eye for long, leading to low efficacy (Dave *et al.*, 2013; Mujoriya & Kshirsagar, 2016). This requires frequent local instillation of drugs, which causes an undesirably high concentration of drug or preservative at the site of action (Kumar & Sharma, 2013). This is also inconvenient for patients and can lead to poor patient compliance (Valarmathi *et al.*, 2017). Hence, there was a need to formulate a controlled ocular delivery system.

Pharmaceutical professionals believe that delivering ophthalmic medications is the most interesting and difficult task. The capacity to sustain a therapeutic level of the drug at the site of action for a long time is one of the primary obstacles in ocular therapy (Gajanan *et al.*, 2017). The fabrication of an effective ocular drug delivery system is necessary in light of the advent of more sensitive diagnostic techniques (A. Mandal *et al.*, 2019). New developments are required for ocular drug delivery systems to establish an extended time and controlled release method in order to overcome the drawbacks of conventional ocular dosage forms (Hardainiyan *et al.*, 2017; Virmani *et al.*, 2023). The goal of recent

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efforts was to create a formulation with improved ocular retention and effective drug concentrations at the intended site of action (Kulhari *et al.*, 2011). Numerous studies have unveiled the potential of using nanoparticles as ocular delivery vehicles for augmentation of drug bioavailability (M. S. Baig *et al.*, 2020b). Nanoparticles can be a viable replacement for eye drops in addition to offering a controlled release method. By formulating ocuserts for ophthalmic medication, patient adherence to the treatment could be enhanced as it eliminates the need for frequent dosing, and it also improves the drug's bioavailability and efficacy (Onugwu *et al.*, 2023). Ocular inserts, or ocuserts, are sterile preparations, shields, or rod shapes fabricated from suitable polymeric materials that can fit into the upper or lower fornix of the eye (Patel *et al.*, 2012). These inserts remain in the anterior part of the eye for an extended period, leading to higher availability of drugs compared to conventional ophthalmic dosage forms (Shanmugam *et al.*, 2016; Shah *et al.*, 2022).

Ciprofloxacin is a potent broad-spectrum, 8-methoxy derivative of the fluoroquinolone group of synthetic antibiotics (Alzahrani *et al.*, 2023). It works by blocking type II topoisomerases (DNA gyrase) and topoisomerase IV, which are important enzymes for separating bacterial DNA and unwinding it. Consequently, this halts the process of bacterial cell division. (Youssef *et al.*, 2021). It is useful in the treatment of eye infections such as bacterial blepharitis, conjunctivitis, keratitis, and keratoconjunctivitis caused by many Gram-positive and Gram-negative aerobic pathogens. In the present study, occuserts loaded with CIP nanoparticles are formulated to combine the benefits of nano-based drug delivery with the effectiveness of occuserts (Youssef *et al.*, 2021; Patil *et al.*, 2023).

Material and Method

Materials

Chemicals: Ciprofloxacin HCL and Eudragit RL PO was kind gift from Medley Pharmaceuticals Ltd Mumbai, Tween 80, Propylene glycol, Carboxymethyl Cellulose (CMC), Dichloromethane (DCM), Sodium chloride, Sodium hydrogen carbonate, Calcium chloride were of Analytical grade.

Instruments: Probe Sonicator, Micro centrifuge, Hot air oven, UV Spectrohotometer, UV chamber, Magnetic stirrer, Incubator.

Preparation of Ciprofloxacin calibration Curve for UV

100 mg of Ciprofloxacin was precisely weighed and transferred to a 100 ml volumetric flask, then filled with pH 7.4 STF to make the final volume. 1 ml of the prepared stock solution was taken and transferred to 100 ml volumetric flask. Again, make up the volume to a 100 ml with STF. Solution C is prepared by taking different concentrations (1 - 5 µg/mL) of solution B in a 10 ml volumetric flask and making up the volume with STF. Each concentration sample was collected, and the absorbance at 278 nm was evaluated using a UV spectrophotometer with pH 7.4 STF as a blank. The graph was drawn by plotting concentration vs absorption, and the plot emerged as a straight line; the linearity was validated using the $y= mx +c$ formula (Uncu *et al.*, 2019).

Preparation of Ciprofloxacin HCl Nanoparticles

The method relied on emulsifying a polymeric organic solution into an aqueous phase, then allowing the organic solvent to dissipate. The polymer (Eudragit RLPO) was dissolved in dichloromethane (DCM). The aqueous phase comprises a surfactant (Tween 80) solution, which is used to emulsify the organic phase. Ciprofloxacin and Tween 80 were dissolved in distilled water to create the aqueous phase. Organic phase was slowly added to aqueous phase during probe sonication. The probe sonication was done for 12 minutes; it was then kept on a magnetic stirrer for 3 hours to evaporate DCM. Then the resultant dispersion was kept on a bath sonicator for 40 minutes and filtered using Whattmann filter paper to remove gritty particles (Dillen *et al.*, 2006). The composition of the formulation is shown in Table 1.

Table 1. Formulation of Ciprofloxacin HCl nanoparticles

Batch no.	Ciprofloxacin (g)	Tween 80 (ml)	Eudragit RLPO (g)	D.W (ml)
F1	0.25	2	0.4	50
F2	0.25	5	0.4	50
F3	0.25	7	0.4	50

Propylene glycol served as the plasticizer and CMC served as the film-forming substance when creating occuserts using the solvent casting technique (Karmakar *et al.*, 2022; Said *et al.*, 2023). CMC was added to the aqueous dispersion of the polymeric nanoparticle formulation (F2) and kept on a magnetic stirrer at 200 rpm for 20 min. Propylene glycol was added as a plasticizer. The mixture was cast in a petri dish and dried in a hot air oven at 50°C for 4 hours. Ocuserts were crafted using a cork borer. The ocuserts were kept in an airtight container at room temperature (Parveen & Joshi, 2020).

Evaluation of Nanoparticles

Particle size and PDI

Nanoparticles are analyzed for their particle size by the Horiba SZ-100 Series. It measures particles in the range of 0.3nm to 10 µm. Measurement of particle size is based on the mechanism of Dynamic Light Scattering (DLS) (Baig, *et al.*, 2020; Wu *et al.*, 2023).

Entrapment efficiency

To remove any free drugs, 2ml of nanoparticle dispersion was taken into Ultrafilteration tube and centrifuged at 2000 rpm for 1 hr. The solution containing the free drug in Ultrafilteration tube is taken and diluted with STF (M. S. Baig *et al.*, 2020a). Absorbance is measured by a UV Spectrophotometer at 278 nm. Using the following equation, the amount of drug that was entrapped in Nanoparticles was determined (Abul Kalam *et al.*, 2013; Chandana *et al*., 2021). Figure 1 shows ultra-filter used for the entrapment efficiency study.

$$\text{Entrapment efficiency (EE\%)} = \frac{\text{Initial Drug Concentration} - \text{Free Drug Concentration}}{\text{Initial Drug Concentration}} \times 100$$

In vitro drug release study

The dialysis membrane bag (Abron Visking semipermeable membrane) was immersed in STF medium (pH 7.4) for one hour prior to use. The dialysis bag was filled with nanoparticle dispersion and submerged in a beaker with 50 ml of STF pH 7.4. It was swirled at 50 rpm and kept at room temperature. To prevent the media in the beaker from evaporating, it was covered. Aliquots (1mL) were removed at periodic intervals (0.25, 0.50, 1, 2, 3) and substituted with a fresh STF medium. With an UV - visible Spectrophotometer set at 278 nm, the samples were evaluated (Liu *et al.*, 2011).

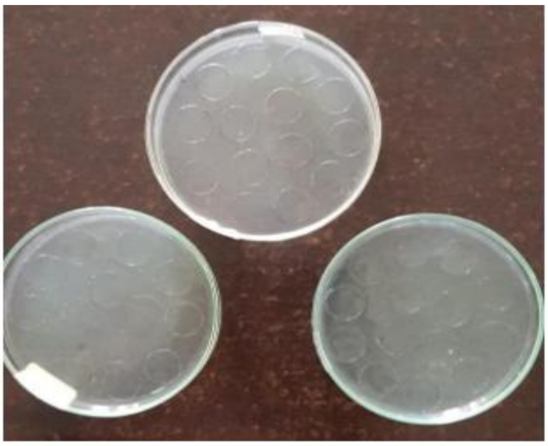


Figure 1: Ultrafiltration tube where nanoparticles were filtered from medium (left), Petridish containing ocusert formulation embedded with drug loaded nanoparticles (right).

Evaluation of Ocusert

Weight variation

This was developed in order to make sure that each film included the same quantity of a medicament without any notable variations. For weight uniformity, three ocuserts were taken randomly from each batch, and their weights were determined using a digital weighing balance, and the mean was calculated (Nautiyal *et al.*, 2012).

Thickness

To achieve a consistent distribution of the therapeutic compounds, the thickness of the ocusert was measured. A micrometer screw gauge was used to measure the thickness uniformity by taking three ocuserts from each batch from different points of the film, and the mean thickness was determined (Hardainiyan *et al.*, 2017).

Folding endurance

To test an ocular inserts resistance to folding, folding endurance is assessed. This further suggests fracture toughness. Folding resistance was assessed by repeatedly folding the film until it broke while holding it between the index and thumb fingers. The folding endurance is the number of folds it can withstand before breaking (Kalyanwat *et al.*, 2016)

Surface pH

The ocuserts were subjected to swelling in 0.1 ml of distilled water for a period of thirty minutes at room temperature in a closed petri dish. pH paper was used to determine the pH (Maheswara Reddy *et al.*, 2011).

Drug content

Three inserts that were carved out of each film were used to evaluate the drug's homogeneity throughout the circular films. The ocuserts were taken from each batch and dissolved in 10 ml 0f STF (pH - 7.4) in a beaker. A 10-milliliter volumetric flask had been filled with 1 ml of the aforementioned solutions and the residual quantity was modified with STF. At 278 nm, a UV-VIS Spectrohotometer was employed to determine absorbance (Shanmugam *et al.*, 2016).

Disintegration time

Ocuserts were placed in 2ml of Simulated Tear Fluid (pH - 7.4) . The amount of time needed for the film to disintegrate was noted (Jiao *et al.*, 2017).

Sterility testing

Preparation of Soyabean Caesin Digestive Media: 4 g of SCBD media was suspended in 100 ml of distilled water. Boil to dissolve the medium completely. After that, the media is autoclaved for 15 minutes at 121°C to sterilize it. SCBD was used to detect the presence of viable forms of bacteria, fungi, or yeast (Shanmugam *et al.*, 2017; Jadhav *et al.*, 2023). Sterilization of ocuserts: The ocuserts were sterilised by subjecting them to UV radiation for 1 hour. The glassware was sterilized in a hot air oven at 170°C for 30 minutes. Test procedure: The sterilised ocuserts were directly inoculated aseptically in the above medium and incubated at 37°C for not less than 7 days. Throughout the incubation phase, the medium was visually inspected for microbial growth at specific intervals (Shanmugam *et al.*, 2017).

Results and Discussion

Calibration Curve

The STF created the CIP HCl drug's calibration curve. The curve's linearity demonstrated that the Beer Lambert's law was followed in the range of concentrations of 1 to 5 µg/ml at lambda maximum of 278 nm. The regression coefficient was determined to be 0.9973. The outcomes were represented graphically in Figure 2.

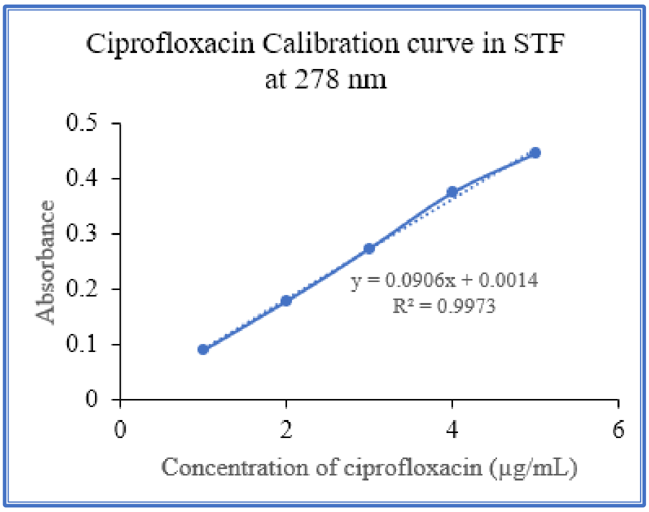
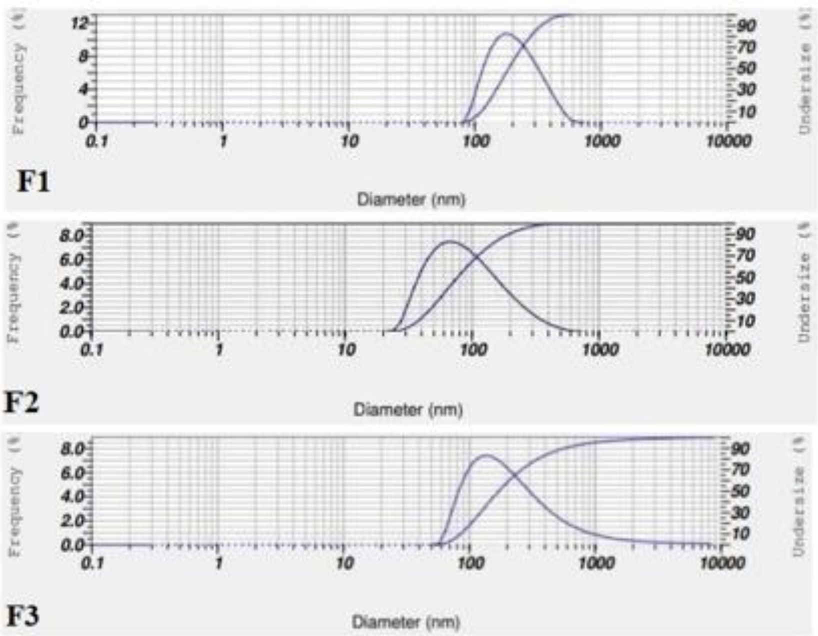


Figure 2. Ciprofloxacin Calibration curve

Particle size and PDI of nanoparticles

Earlier, while preparing nanoparticles, when it was sonicated for 12 minutes, the particle size came out to be greater than 2000 nm. Afterwards, when we increased the sonication time to 50 min, the particle size of all the formulations came out to be below 500 nm. PDI was also reduced from more than 3 to less than 1, which indicates the formation of a stable nanoemulsion and that the duration of sonication has a significant effect on particle size. NPs containing 2 mL and 7 mL of tween 80 have particle sizes below 100 nm, which is helpful for efficient drug delivery (Hajwani *et al.*, 2023). Results are shown in Figure 3.



Particle Properties	F1	F2	F3
Particle size (nm)	74.8	384.3	78.2
PDI	0.876	0.257	0.710

Figure 3: Figure indicating graph and table of particle size evaluation for nanoparticles formulation F1-F3

Entrapment efficiency

Studies have shown that Tween80 is more readily adsorbed as its quantity is raised, which results in a reduction of the surface tension of polymers, an increase in the particle size of NPs, and an improvement in encapsulating efficiency. The EE% of F1 was 57%, which was increased to 74.96% in F2. However, when we increase the concentration of tween 80 to 7 mL, there is a decrease in entrapment efficiency. The results are mentioned in Table 2.

In-vitro drug release

Formulations were shown to be efficient at prolonging the release profile for up to 24 hours in an in vitro drug release assay. Formulation F2 demonstrated the highest drug release of 56.34%, whereas formulation F1 had a drug release of 49.34% at the completion of 3 hours. Figure 4 shows the proportion of medication release for all 3 formulations.

Weight variation of occusert

The weight of ocuserts was found to be in the range of 0.0076 gm to 0.0093 gm. Films were weighed, and observations of film mass with low SD values indicate the uniformity and equal distribution of excipients in ocuserts.

Thickness of the occuser

The results show that there were no noticeable differences in the thickness of the inserts, indicating that the product's ingredients were distributed uniformly. The formed ocuserts' thickness ranges from 0.20mm to 0.19mm.

Drug Content in the Occurrence

The range of drug content was 87% to 93%. For all of the preparations, there was good consistency in the medication content between batches. According to the results of the content uniformity assessment of the preparations made, the method used to make the ocuserts in this study was able to make films with a consistent drug concentration and little batch variation.

Surface pH of the occuser

Three occuserts from each batch have been tested to determine the surface pH; they all had pH values between 6 and 7, demonstrating that they won't trigger any issues or discomfort when placed in the eye's cul-de-sac.

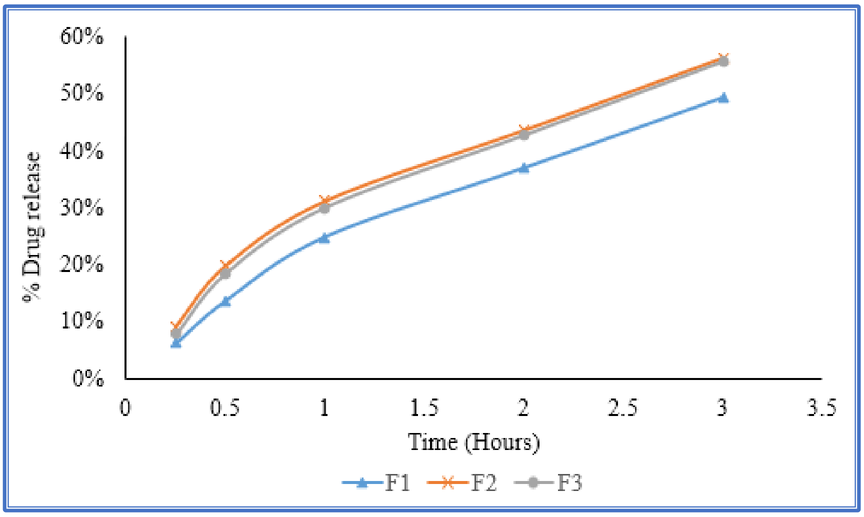


Figure 4: Drug release study

Table 2. Result of evaluation of Ocusert

Ocusert Evaluation	Result
Weight variation	0.0076 gm
Thickness	0.20 mm
Drug content	93%
Surface pH	6-7
Disintegration time	4 min 30 sec
Folding Endurance	>300

Disintegration time of occusert

The disintegration time of all the ocusert is found to be between 4 and 5 min, which indicates the amount of time required by the ocusert to release nanoparticles into the cul-de- -sac of the eye

Folding Endurance of occusert

The ocusert's folding durability was individually assessed, and the insert showed no signs of cracking after 300 folds, indicating good flexibility of the ocuserts.

Sterility test of occusert

Incubated samples were observed after a week. The control and test samples were found to be free of microbial growth. The results confirm the sterility test of the prepared ocusert formulation.

Conclusion

According to the current investigation, all the formulations have achieved the goals of the study, and the ocusert loaded with CIP nanoparticles is able to illustrate sustained drug release with optimum particle size, PDI, entrapment efficiency, drug content, folding endurance, and so on. Out of three formulations, F2 of nanoparticles embedded in ocusert was found to be the best since it has a particle size below 500nm and a PDI below 0.5, which indicates greater stability and delivery of nanoparticles. F2 also has a 74.96% entrapment efficiency, which is greater than the other two formulations. Hence, the combination method of nanoparticles in ocusert can be employed for the administration of ocular drugs. The improved formulations' nanoparticle-loaded ocuserts provided sustained drug delivery, which meant that the dose had to be given less often over the course of 24 hours. Consequently, a formulation that has been optimized may promote patient compliance.

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Conflict of interest:

No conflict of interests.

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